Amendments to the Specification

Please replace the third paragraph on page 62, beginning with line 16, with the following amended paragraph:

TIE-2 Enzyme assay (TIE2-E)

The TIE-2 enzyme assay uses the LANCE method (Wallac) and GST-TIE2, baculovirus expressed recombinant constructs of the intracellular domains of human TIE2 (amino acids 762-1104, GenBank Accession # L06139) tagged by GST). The method measures the ability of the purified enzymes to catalyse the transfer of the γ-phosphate from ATP onto tyrosine residues in a biotinylated synthetic peptide, D1-15 (biotin-C6-LEARLVAYEGWVAGKKKamide) (SEQ ID NO: 1). This peptide phosphorylation is detected using the following procedure: for enzyme preactivation, GST-TIE2 is incubated for 30mins at room temperature with 2 mM ATP, 5 mM MgCl2 and 12.5 mM DTT in 22.5 mM HEPES buffer (pH7.4). Preactivated GST-TIE2 is incubated for 30mins at room temperature in 96 well plates with 1 uM D1-15 peptide, 80 uM ATP, 10 mM $MgCl_2$, 0.1mg/ml BSA and the test compound (diluted from a 10 mM stock in DMSO, final DMSO concentration is 2.4%) in 1 mM HEPES (pH7.4). The reaction is stopped by the addition of EDTA (final concentration 45 mM). Streptavidin linked-APC (allophycocyanin, Molecular Probe) and Europium-labeled anti-phosphorylated tyrosine antibody (Wallac) are then added at the final concentration of 17 ug/well and 2.1 ug/well, respectively. The APC signal is measured using an ARVO multilabel counter. (Wallac Berthold Japan). The percent inhibition of activity is calculated relative to blank control wells. The concentration of test compound that inhibits 50% of activity (IC_{50}) is interpolated using nonlinear regression (Levernberg-Marquardt) and the equation, $y = Vmax\ (1-x/(K+x)) + Y2$, where "K" is equal to the IC_{50}. The IC_{50} values are converted to pIC_{50} values, i.e., -log IC_{50} in Molar concentration.

Please replace the second paragraph on page 63, beginning with line 7, with the following amended paragraph:

TIE-2 Enzyme assay (TIE2-E2

The TIE-2 enzyme assay uses the LANCE method (Wallac) and GST-TIE2, baculovirus-expressed recombinant constructs of the intracellular domains of human

TIE2 (amino acids 762-1104, GenBank Accession # L06139) tagged by GST). The method measures the ability of the purified enzymes to catalyse the transfer of the γ-phosphate from ATP onto tyrosine residues in a biotinylated synthetic peptide, D1-15 (biotin-C6-LEARLVAYEGWVAGKKKamide) (SEQ ID NO: 1). This peptide phosphorylation is detected using the following procedure: for enzyme preactivation, GST-TIE2 is incubated for 2 hours at room temperature with 80 μM ATP, 10 mM $MgCl_2$, 0.1 mg/ml BSA, 0.01% Tween 20 and 1 mM DTT in 100 mM HEPES buffer (pH7.4). 5nM preactivated GST-TIE2 is incubated for 2 hours at room temperature in 96 well plates with 1 uM D1-15 peptide, 80 uM ATP, 10 mM MgCl2, 0.1mg/ml BSA, 0.01% Tween 20 and titrated test compound (diluted from a 10 mM stock in DMSO, final DMSO concentration is 2.4%) in 100 mM HEPES (pH7.4). The reaction is stopped by the addition of EDTA (final concentration 45 mM). Streptavidin linked-APC (allophycocyanin, PerkinElmer) and europium-labeled anti-phosphotyrosine antibody (PerkinElmer) are then added at the final concentration of 8 nM and 1nM, respectively. The APC signal is measured using an Wallac Multilabel 1420 counter. (Wallac Berthold Japan). The percent inhibition of activity is calculated relative to blank control wells. The concentration of test compound that inhibits 50% of activity (IC_{50}) is interpolated using nonlinear regression (Levernberg-Marquardt) and the equation, y = Vmax (1-x/(K+x)) + Y2, where "K" is equal to the IC_{50}. The IC_{50} values are converted to pIC_{50} values, i.e., -log IC_{50} in Molar concentration.

Please replace the first and second paragraphs on page 65, beginning with line 1, with the following amended paragraphs:

Assay conditions: The final assay conditions are 50mM HEPES, pH 7.5, 5% DMSO (when screening compounds), 200μM ATP, 5mM $MgCl_2$, 1mM DTT, 50μM sodium vanidate, 1nM activated enzyme, and 200μM peptide. IC_{50}'s of compounds are measured under subsaturating ATP (200μM) and varying concentrations of activated Tie2 and peptide substrate (RFWKYEFWR-OH; MW 1873 Da, TFA salt) (SEQ ID NO: 2). Panvera Anti-phosphotyrosine antibody (Cat#P2840) and PTK Green Tracer (Cat#P2842) are used to detect the phosphorylated peptide. Polarization is measured on a TECAN Polarion in 138-second cycles for 30 minutes at room

temperature. IC_{50}'s are then determined from the % polarization using normal calculation methods. The IC_{50} values are converted to pIC_{50} values, i.e., -log IC_{50} in Molar concentration.

VEGF-R2 enzyme assay (VEGF-E): The VEGF enzyme assay uses the LANCE method (Wallac) and GST-VEGFR2, baculovirus expressed recombinant constructs of the intracellular domains of human TIE2 tagged by GST. The method measures the ability of the purified enzymes to catalyse the transfer of the γ-phosphate from ATP onto tyrosine residues in a biotinylated synthetic peptide, (biotin-aminohexyl-EEEEYFELVAKKKK-NH2) (SEQ ID NO: 3). This peptide phosphorylation is detected using the following procedure: GST-VEGFR2 is incubated for 40-60 mins at room temperature with 75uM ATP, 5 mM MgCl2, 0.1mM DTT, 0.1mg/mL BSA and the test compound (diluted from a 10 mM stock in DMSO for desired concentration) in 100 mM HEPES buffer. The reaction is stopped by the addition of EDTA (final concentration 50 mM). Streptavidin linked-APC (allophycocyanin, Molecular Probe) and Europium-labeled anti-phosphorylated tyrosine antibody (Wallac) are then added at the final concentration of 15nM and 1nM, respectively. The APC signal is measured using an ARVO multilabel counter (Wallac Berthold, Japan). The percent inhibition of activity is calculated relative to blank control wells. The concentration of test compound that inhibits 50% of activity (IC_{50}) is interpolated using nonlinear regression (Levernberg-Marquardt) and the equation, $y = V_{max} (1-x/(K+x)) + Y2$, where "K" is equal to the IC_{50}. The IC_{50} values are converted to pIC_{50} values, i.e., -log IC_{50} in Molar concentration.

Please replace the last paragraph on page 65, beginning with line 29 and ending on page 66, line13, with the following amended paragraph:

VEGF-R2 enzyme assay (VEGF-E2): The VEGF enzyme assay uses the LANCE method (Wallac) and GST-VEGFR2, baculovirus expressed recombinant constructs of the intracellular domains of human TIE2 tagged by GST. The method measures the ability of the purified enzymes to catalyse the transfer of the γ-phosphate from ATP onto tyrosine residues in a biotinylated synthetic peptide, (biotin-aminohexyl-EEEEYFELVAKKKK-NH2) (SEQ ID NO: 3). This peptide phosphorylation is detected using the following procedure: GST-VEGFR2 is incubated for 40-60 mins at room temperature with 75uM ATP, 5 mM $MgCl_2$, 0.1mM

DTT, 0.1mg/mL BSA and the test compound (diluted from a 10 mM stock in DMSO for desired concentration) in 100 mM HEPES buffer. The reaction is stopped by the addition of EDTA (final concentration 50 mM). Streptavidin linked-APC (allophycocyanin, Molecular Probe) and Europium-labeled anti-phosphorylated tyrosine antibody (Wallac) are then added at the final concentration of 15nM and 1nM, respectively. The APC signal is measured using an ARVO multilabel counter (Wallac Berthold, Japan). The percent inhibition of activity is calculated relative to blank control wells. The concentration of test compound that inhibits 50% of activity (IC_{50}) is interpolated using nonlinear regression (Levernberg-Marquardt) and the equation, $y = V_{max}$ (1-x/(K+x)) + Y2, where "K" is equal to the IC_{50}. The IC_{50} values are converted to pIC_{50} values, i.e., -log IC_{50} in Molar concentration.

Please replace the second paragraph, beginning on line 10, with the following amended paragraph:

The substrate phosphorylation assays use the VEGFR3 catalytic domain, which is expressed in *Sf. 9* insect cells as an amino-terminal GST-tagged fusion protein. The catalytic domain of human VEGFR3 (AA residues #819-1298 based upon GenBank Accession #XM003852) is cloned by PCR from human Placenta Marathon Ready cDNA (Clontech). The PCR product is subcloned into pFastBac1 vector containing an N-terminal GST tag. The resulting pFB/GST/VEGFR3icd vector is used to generate a recombinant baculovirus for protein expression. The VEGFR3 catalytic domain translated sequence is:
MSPILGYWKI KGLVQPTRLL LEYLEEKYEE HLYERDEGDK
WRNKKFELGL EFPNLPYYID GDVKLTQSMA IIRYIADKHN MLGGCPKERA
EISMLEGAVL DIRYGVSRIA YSKDFETLKV DFLSKLPEML KMFEDRLCHK
TYLNGDHVTH PDFMLYDALD VVLYMDPMCL DAFPKLVCFK
KRIEAIPQID KYLKSSKYIA WPLQGWQATF GGGDHPPKSD LLVPRGSPEF
KGLPGEVPLE EQCEYLSYDA SQWEFPRERL HLGRVLGYGA
FGKVVEASAF GIHKGSSCDT VAVKMLKEGA TASEQRALMS ELKILIHIGN
HLNVVNLLGA CTKPQGPLMV IVEFCKYGNL SNFLRAKRDA
FSPCAEKSPE QRGRFRAMVE LARLDRRRPG SSDRVLFARF
SKTEGGARRA SPDQEAEDLW LSPLTMEDLV CYSFQVARGM
EFLASRKCIH RDLAARNILL SESDVVKICD FGLARDIYKD PDYVRKGSAR
LPLKWMAPES IFDKVYTTQS DVWSFGVLLW EIFSLGASPY PGVQINEEFC

QRLRDGTRMR APELATPAIR RIMLNCWSGD PKARPAFSEL VEILGDLLQG RGLQEEEEVC MAPRSSQSSE EGSFSQVSTM ALHIAQADAE DSPPSLQRHS LAARYYNWVS FPGCLARGAE TRGSSRMKTF EEFPMTPTTY KGSVDNQTDS GMVLASEEFE QIESRHRQES GFR (SEQ ID NO: 4).